DIAGNOSTICS

COVID-19 diagnostics in context

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The coronavirus disease 2019 (COVID-19) pandemic has highlighted the need for different types of diagnostics, comparative validation of new tests, faster approval by federal agencies, and rapid production of test kits to meet global demands. In this Perspective, we discuss the utility and challenges of current diagnostics for COVID-19.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The median incubation period of SARS-CoV-2 is ~5 days (ranging from 2 to 14 days), and people who develop symptoms do so within ~12 days of infection (ranging from 8 to 16 days) (*1*). A sizable portion of person-to-person virus transmission may occur before infected individuals develop symptoms (presymptomatics) (*2*). A fraction of infected individuals never develop symptoms (asymptomatics) yet may contribute substantially to disease transmission (*3*). Nucleic acid tests (NATs) can diagnose SARS-CoV-2 infection and are typically used after the onset of symptoms. The kinetics and sensitivity of testing among asymptomatic people remain uncharacterized. The recovery period for mild cases of COVID-19 is ~2 weeks and that for severe cases is ~6 weeks. In the most severe cases, the time from symptom onset to death ranges between 2 and 8 weeks.

Large-scale diagnostic testing is a key tool in epidemiology and in containing outbreaks such as COVID-19. Among other measures, aggressive testing might have helped restrain the coronavirus in the United States as it did in Hong Kong, Singapore, and Taiwan. Technical uncertainties in testing, initial regulatory hurdles, limited resources, and disruptions to supply chains permitted the spread of the virus worldwide. These challenges may be more pronounced in low- and middle-income countries. This Perspective addresses some of the key concerns regarding diagnostics that have arisen during the recent COVID-19 pandemic. An accompanying infographic (fig. S1) details available diagnostic tests, their applications, and areas for future developments; a continuously updated version of this infographic is accessible at https://csb.mgh.harvard.edu/covid.

TYPES OF TESTS

COVID-19 tests can be grouped as nucleic acid, serological, antigen, and ancillary tests, all of which play distinct roles in hospital, point-of-care, or large-scale population testing. Table 1 summarizes the existing and emerging tests, current at the time of writing (May 2020). A continuously updated version of this table is available at https://csb.mgh.harvard.edu/covid. In NATs, viral RNA is reverse-transcribed into DNA, which is then amplified through polymerase chain reaction (PCR). NATs are the most widely used tests for detection of SARS-CoV-2 (the virus that causes COVID-19) and are increasingly run on automated platforms that take several hours to complete (*4*). The U.S. Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) have recommended distinct SARS-CoV-2–specific RNA regions for testing (viral nucleocapsid N1, N2, and human RNase *P* gene), primers, and reagents (*5*). This assay differs from the World Health Organization (WHO) assay, which targets the CoV-2 RNA-dependent RNA polymerase (*RdRP*) and envelope (*E*) genes (*6*). By May 2020, more than 100 U.S. public health laboratories had completed the CDC's verification process and started offering NATs. These assays, including those from cleared commercial vendors, have high analytic sensitivity and specificity for SARS-CoV-2 if sample acquisition, preparation, and device operation are carried out by trained personnel.

Serological tests rely on affinity ligands to assess host response proteins [host immunoglobulin G (IgG), IgM, interleukins, and other host components]. Most IgG/IgM serum tests use recombinant viral proteins or peptides harvested from *Escherichia coli* or human embryonic kidney (HEK) 293 cells as capture reagents for human IgG/IgM. These tests need to accurately distinguish past infections due to SARS-CoV-2 from those caused by other human coronaviruses. The uses of serological testing include determination of previous viral exposure in the population for retrospective assessment of the efficacy of control measures, assessment of immune status for individuals, and determination of surrogates of immunity for vaccine development. Each of these uses places different constraints on diagnostics.

Most antigen tests probe for the nucleocapsid (N) or spike (S) proteins of SARS-CoV-2 via lateral flow or ELISA (enzyme-linked immunosorbent assay) tests. These tests can be performed using nasopharyngeal swabs and take less than an hour to complete. Ancillary tests comprise a broad category of personal devices (apps and wearable sensors) and hospital laboratory tests, including blood gas analysis, coagulation tests, and indicators of cytokine storm (*7*) such as interleukin-6 (IL-6), ferritin, granulocyte colony-stimulating factor (G-CSF), macrophage inflammatory protein–1α (MIP-1α), and tumor necrosis factor–α (TNF-α). These tests aid in the management of patients with COVID-19.

CROSS-REACTIVITY, CROSS-IMMUNITY, ACCURACY, AND TURNAROUND TIME OF TESTS

SARS-CoV-2 is a β-coronavirus causing the current COVID-19 outbreak and is the seventh coronavirus that is known to infect humans. Several related viruses have been described, including SARS-CoV-1, a β-coronavirus that caused the 2002 SARS outbreak in China; MERS, a β-coronavirus that caused the Middle East respiratory syndrome outbreak beginning in Jordan in 2012; and 229E, OC43, HKU1, and

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Table 1. Performance comparison of different test types. Throughput is determined by process type and assay time. In general, automated plate-based assays have higher daily throughputs. Hashtag (#) indicates example systems that have received FDA emergency use authorization (FDA-EUA). See https://csb.mgh.harvard.edu/covid to access continuously updated information. PCR, polymerase chain reaction; PCR-POC, PCR–point-of-care; ddPCR, digital droplet PCR; NEAR, nicking endonuclease amplification reaction; RCA, rolling circle amplification; SHERLOCK, specific high-sensitivity enzymatic reporter; DETECTR, DNA endonuclease-targeted CRISPR transreporter; NGS, next-generation sequencing; μNMR, micro–nuclear magnetic resonance; LFA, lateral flow assay; ELISA, enzyme-linked immunosorbent assay; CLIA, chemiluminescence immunoassay; EIA, enzyme immunoassay; ECLIA, electrochemiluminescence immunoassay; ECS, electrochemical sensing; VAT, viral antigen assay; IFM, immunofluorescence microscopy; WB, Western blot.

Type	Target	Virus	Assay time	Process type	FDA-EUA	Examples
PCR	Viral RNA	SARS-CoV-2	2–8 hours; >12 hours	Plate	56	#Roche, #LabCorp, #BioMerieux, #Qiagen, #Perkin-Elmer, #Becton Dickinson, #Luminex, #Thermo Fisher, others
PCR-POC	Viral RNA	SARS-CoV-2	<1 hour	Cartridge	2	#Cepheid, #Mesa, Credo
ddPCR	Viral RNA	SARS-CoV-2	2–4 hours	Manual	1	#BioRAD
NEAR	Viral RNA	SARS-CoV-2	15 min	Cartridge	1	#Abbott
OMEGA	Viral RNA	SARS-CoV-2	1 hour	Plate	1	#Atila BioSystems
RCA	Viral RNA	SARS-CoV	2 hours		0	
SHERLOCK	Viral RNA	SARS-CoV-2	1.5 hours	Kit	1	#Sherlock Biosciences (CAS13a)
DETECTR	Viral RNA	SARS-CoV-2	1 hour	Kit	0	Mammoth Biosciences (CAS12a)
NGS	Viral RNA	SARS-CoV-2	Days		1	#IDbyDNA, Vision, Illumina
μNMR	Viral RNA	SARS-CoV-2	2 hours	Cartridge	0	T2 Biosystems
LFA	IgG, IgM	SARS-CoV-2	15 min	Cartridge	3	#Cellex, #Sugentech, #ChemBio, Innovita
ELISA	IgG, IgM	SARS-CoV-2	2–4 hours	Plate	4	#Mount Sinai, #Ortho-Clinical (2), #EUROIMMUN US Inc., BioRAD, Snibe, Zhejiang orient, Creative Dx
CLIA	IgG, IgM	SARS-CoV-2	30 min	Cartridge	2	#Abbott, #DiaSorin
EIA	IgG, IgM	SARS-CoV-2	2 hours	Plate	1	#BioRAD
MIA	IgG, IgM	SARS-CoV-2		Plate	1	#Wadsworth Center
ECLIA	IgG, IgM	SARS-CoV-2	20 min	Plate	1	#Roche
ECS	IgG, cytokine	SARS-CoV-2	1 hour	Cartridge	0	Accure Health
VAT	Viral antigen	SARS-CoV-2	20 min	Cartridge	1	#Quidel, Sona NT, RayBiotech, SD Biosensors, Bioeasy
Microarrays	Ig epitopes	SARS-CoV-2	1.5 hours	Plate	0	RayBiotech, PEPperPRINT
IFM	Viral protein	SARS-CoV	3 hours	Manual	0	
WB	IgG, IgM; viral protein	SARS-CoV	4 hours	Manual	0	

NL63, which are strains of α- and β-coronaviruses that cause a fraction of common colds (*8*). Cross-reactivity in diagnostic tests has been observed. For example, an immunogenic domain in the S protein of SARS-CoV-1 is highly conserved in multiple strains of SARS-CoV-2, and murine monoclonal antibodies raised against the SARS-CoV-1 immunogenic domain recognized the S protein of SARS-CoV-2 (*9*, *10*). Defining whether humans can naturally develop cross-immunity requires investigation (*11*). At present, studies using

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sera from individuals who have recovered from SARS or COVID-19 infections have shown limited cross-neutralization, suggesting that recovery from one infection does not protect against the other (*12*).

The accuracy of a diagnostic test is commonly defined by its sensitivity (positive test in a patient with disease), specificity (negative test in a healthy individual), negative predictive value (chance that a person with a negative test is truly disease-free), and positive predictive value (chance that a person with a positive test is truly diseased). NATs typically have high analytical sensitivities and specificities under ideal circumstances. However, in clinical reality, the test sensitivity varies according to duration of illness, the specific clinical COVID-19 syndrome, the site of specimen collection, the quality of specimen collection, and the viral load. As a result, false-negative rates have been reported to occur in ~30% of patients with COVID-19 [range, 10 to 40% (*13*, *14*)]. If there is a high pretest probability in patients with symptoms or findings (suggestive computed tomography scans or chest x-rays), testing should be repeated after a single negative result. By contrast, concerns about "missing cases" that are infectious in the community because of imperfect sensitivity are outweighed by the current lack of access to testing.

The accuracy of serological tests can be near 100% when samples are acquired 20 days after infection or first symptoms. At earlier time points, the sensitivity and specificity are lower as the immune response is evolving. A few established companies have rolled out tests with high diagnostic accuracies, but many others show poor performance. Inaccurate serological tests may lead to two major problems: the false labeling of patients who have been infected as disease-negative, and the false labeling of patients who have not been infected as disease-positive. Both errors will affect control efforts in important ways and have consequences for individuals tested. Test inaccuracy is not entirely surprising because the FDA loosened its standards in mid-March and allowed companies to sell antibody tests without submitting clinical evidence that the tests worked (*15*). This decision was reverted in mid-April when the FDA changed its position and mandated proof of efficacy. Irrespective of company-submitted accuracy data, there is a need to independently verify the accuracy of serological tests in the field. The Infectious Disease Society of America recently released guidelines for such antibody testing (*16*). A consortium of scientists from the University of California San Francisco, the University of California Berkeley, the Chan Zuckerberg Biohub, and the Innovative Genomics Institute has begun to compare commercially available tests (*17*). The Foundation for Innovative New Diagnostics (FIND), a Geneva-based not-for-profit organization, is collecting evaluations of COVID-19 molecular tests and immunoassays, in collaboration with the WHO and other partners (*18*).

The time from sample acquisition to NAT result can vary from less than an hour to several days. Factors that determine this time include the testing platform as well as the logistics of sample acquisition, transport, processing, and reporting. NATs based on conventional PCR typically require 4 to 6 hours of processing, including sample preparation, RNA extraction, reverse transcription PCR (RT-PCR), and readout of amplified DNA products. Point-of-care PCR kits can shorten the time to result to about 30 min (*19*) and can be occasionally faster (*20*). This is accomplished using cartridges or lateral flow technology for sample preparation, nucleic acid amplification, and detection. However, these rapid tests typically have lower throughput, are not yet automated, and are generally more expensive than other tests. In modern healthcare systems, there are different needs and requirements for different types of assays, for example, for screening large populations versus making rapid clinical decisions.

UNDERSTANDING VIRAL LOAD AND IMMUNITY

SARS-CoV-2 infection triggers innate and adaptive immune responses, which can be detected in peripheral blood. Extensive efforts are under way to characterize these immune responses longitudinally in patients with diverse clinical outcomes. Results from these studies should help explain how the body controls the infection and why it sometimes fails to do so. Among adaptive immune cells, B cells are of interest because some of them may produce IgM or IgG antibodies that recognize SARS-CoV-2 antigens (*21*). In this context, a positive titer refers to the detection of SARS-CoV-2–specific antibodies in a patient's serum sample. Seroconversion (the body's process of developing antibodies) may occur around 1 to 2 weeks after infection and is thought to provide some immunity against SARS-CoV-2 in people who recover from the disease. Evidence from other coronaviruses suggests that protection may last for 1 to 2 years; however, at this time, the duration and nature of immunity generated in response to SARS-CoV-2 infection are unknown (*11*), and there is no evidence that COVID-19 antibody–positive patients who have recovered from the disease are protected from a second infection. It is thus advisable that such patients continue wearing personal protective equipment and practicing social distancing and frequent hand washing (*22*).

A complete infectious virus particle consists of nucleic acid surrounded by a capsid. NATs detect viral RNA that may not necessarily come from replicating viruses (*23*). Few studies have published the relationship between cultivatable virus and RNA shedding, and it seems that a large subset of convalescing people who shed RNA may not be infectious (*2*, *11*). These findings require confirmation. The only current test to unequivocally assess the presence of infectious viral particles is viral culture in cells (*24*). Host cells that support growth of SARS-CoV-2 include African green monkey kidney Vero C1008 clone E6 cells (ATCC-CRL-1586).

In addition to antibodies, quantifying the abundance of virus within an infected individual may help inform treatment or outcomes. Viral load (also referred to as viral burden or titer) is a numerical expression of the quantity of virus in a given volume (the number of infectious particles per milliliter). Clinical observations suggest that the initial viral load in an individual is related to the severity of COVID-19 disease. The current evidence of this relationship, however, remains limited by the suboptimal quality of many of the studies, their retrospective nature, small sample sizes, and the potential for selection bias. Another possible source of error is the type of NAT used. At high viral loads, both RT-PCR and digital droplet PCR (ddPCR) show consistent results, whereas for low viral load samples, ddPCR was shown to be more accurate due to its higher sensitivity (*25*); however, this requires confirmation. Also, patients of different ages, including children, may have similar viral loads, raising the possibility that children may be infectious despite typically showing less severe symptoms than adults. In short, more research is required to match viral loads with symptoms, infectiousness, and outcomes. In patients with COVID-19, positive test results determined by NATs have been reported as follows: bronchoalveolar lavage (BAL), 93%; bronchoscopy biopsy, 46%; sputum, 72%; nasal swabs, 63%; pharyngeal swab, 32%; feces, 29%; blood, 1%; and urine, 0% (*26*). These numbers vary in

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other cohorts and depend on the severity of the disease. The viability and infectiousness of the virus in these samples warrant further investigation (*21*, *27*).

TESTING COSTS AND PRIORITIZATION

A new law mandates that Medicare, Medicaid, other government health care and insurance plans, and most private plans cover COVID-19 testing in the United States without copays or deductibles. On 5 March 2020, the Centers for Medicare and Medicaid Services (CMS) announced new Healthcare Common Procedure Coding System (HCPCS) codes for health care providers and laboratories to test patients for SARS-CoV-2. Starting in April, laboratories performing the test could bill Medicare and other health insurers for services, using a newly created HCPCS code (U0001). This code applies to all tests that were developed by the CDC. Laboratories performing non-CDC laboratory tests for SARS-CoV-2 can bill for them using a different HCPCS code (U0002). Current test prices are $35.91 for U0001 and $51.31 for U0002. The overall costs should take into context how a diagnostic test is used in practice. For example, if a test is restricted to very sick patients, the cost is small compared to the overall medical care. Conversely, if a test is used for broad screening, the cost per positive result could be high depending on prevalence.

There are different indications for diagnostic testing for individuals with a proven or suspected case of COVID-19. Given the limited testing capacity in the United States, priority lists have been established. Priority 1 includes hospitalized patients and symptomatic health care workers. Priority 2 includes symptomatic patients in health care facilities, >65-year-old patients with underlying conditions, and first responders. Priority 3 includes symptomatic patients, including critical infrastructure workers. Individuals without symptoms are currently not prioritized for any testing (*28*). Specific use cases for different tests have also been laid out (*29*), but they are likely to change as more testing capabilities become available and societal needs change, such as identification of infectious individuals versus seropositive individuals returning to work.

When carried out broadly and repeatedly, NAT results have consequences for individuals, communities, and the entire population. These tests not only permit the identification, isolation, and treatment of infected individuals but also diagnose presymptomatic and asymptomatic carriers and thus more accurately define the infection rates across populations. Serological testing should be used in parallel with NATs to determine which individuals have acquired immunity and how long it lasts. Serosurveys may also help efforts to develop vaccines. By extension, serological testing that is performed frequently and on a wide scale should help determine what fraction of the population may be immune to COVID-19 and which individuals may rejoin the workforce. The lack of longitudinal testing is problematic because it inhibits our ability to understand the evolution of the disease.

Containing COVID-19 will likely require combinations and concomitant use of the different types of diagnostic tests discussed above. Excitingly, more sensitive and specific kits have become available from major vendors. To be successful, these assays will need to be deployed in such a way that broad and repeated testing becomes routine. Last, there is a need to develop test kits that simplify lengthy purification steps and yield results in much shorter time frames than is currently available. A variety of new approaches are currently being tested experimentally to achieve such results.

SUPPLEMENTARY MATERIALS

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Fig. S1. Infographic.

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